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Changes in winter depression phenotype correlate with white blood cell gene expression profiles: A combined metagene and gene ontology approach

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ABSTRACT

In the present study we evaluate the feasibility of gene expression in white blood cells as a peripheral marker for winter depression. Sixteen patients with winter type seasonal affective disorder were included in the study. Blood was taken by venous puncture at three time points; in winter prior and following bright light therapy and in summer. RNA was isolated, converted into cRNA, amplified and hybridized on Illumina® gene expression arrays. The raw optical array data were quantile normalized and thereafter analyzed using a metagene approach, based on previously published Affymetrix gene array data. The raw data were also subjected to a secondary analysis focusing on circadian genes and genes involved in serotonergic neurotransmission. Differences between the conditions were analyzed, using analysis of variance on the principal components of the metagene score matrix. After correction for multiple testing no statistically significant differences were found. Another approach uses the correlation between metagene factor weights and the actual expression values, averaged over conditions. When comparing the correlations of winter vs. summer and bright light therapy vs. summer significant changes for several metagenes were found. Subsequent gene ontology analyses (DAVID and GeneTrail) of 5 major metagenes suggest an interaction between brain and white blood cells. The hypothesis driven analysis with a smaller group of genes failed to demonstrate any significant effects. The results from the combined metagene and gene ontology analyses support the idea of communication between brain and white blood cells. Future studies will need a much larger sample size to obtain information at the level of single genes.

1. Introduction

DSM-IV-TR defines seasonal affective disorder winter type (in brief: winter depression) as a distinct form of depression with a clear seasonal pattern. It manifests almost yearly in fall/winter and disappears completely in spring/summer. Winter depression is among others characterized by atypical symptoms such as an increased need for sleep and carbohydrate craving and often results in considerable weight gain in the winter period. An epidemiological study has estimated that approximately 3% of the Dutch adult population suffers from winter depression (Mersch et al.,1999). A majority of patients suffering from winter depression responds to antidepressant treatment and in particular to bright light exposure. After the initial report on the beneficial effect of bright light (Rosenthal et al., 1984) various conditions have been investigated in order to optimize therapy (Meesters and Van den Hoofdakker, 1998a,b; Partonen and Magnusson, 2001; Terman et al., 1989,1998; Thompson et al., 1999). Nowadays, bright light therapy (BLT) is the treatment of first choice for winter type SAD in The Netherlands.

In common with other psychiatric disorders, the biological mechanism(s) underlying winter depression and BLT are still not fully understood (LeGates et al., 2014). Several hypotheses have been raised, mostly involving serotonin, the biological clock and the hormone melatonin, but there is still insufficient support from empirical studies (Etain et al., 2011; Koorengevel et al., 2002; Lewy et al., 1987, 1998, 2006; Rosenthal et al., 1988; Wirz-Justice et al., 1993). Yet evidence is accumulating that the interaction between serotonergic, melatonergic and

Abbreviations: BLT, bright light therapy; GO, gene ontology analysis; MEC, Medical Ethical Committee; SCN, suprachiasmatic nucleus

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circadian systems plays an important role in both the etiology and antidepressant treatment of winter depression (Edgar et al., 1993; Prosser et al., 1993; Lewy et al., 2006, for review see Ciarleglio et al., 2011). Moreover, genetic studies found associations of polymorphisms in the SERT gene (Johansson et al., 2003a; Rosenthal et al., 1998; Willeit et al., 2003), the 5-HT_{2A} receptor gene (Lee et al., 2006; Molnar et al., 2010), and the circadian genes PER2, ARNTL and NPAS2 with winter depression (Johansson et al., 2003b; Partonen et al., 2007).

The role of genetics in winter depression can be studied at the level of gene polymorphisms (gene association studies), gene expression (via measurement of mRNA levels), and epigenetic programming. In contrast to gene expression and epigenetic studies, DNA for gene association studies can be taken from virtually every cell in the body and thus samples can be drawn from easily obtainable cells, such as white blood cells. While in principle gene expression and epigenetic approaches can provide information on gene * gene interactions (epistasis) and gene * environment interactions, it is important to note that gene expression and epigenetic status may largely differ between various tissues and cell types.

In the current study we investigated whether changes of winter depression phenotype might correlate with gene expression profiles in white blood cells. Winter depression was chosen because we expected it to be less heterogeneous than major depression. Other factors were its more or less regular pattern and the relatively high efficacy of bright light therapy.

2. Methods

2.1. Ethical considerations

Initially twenty patients diagnosed with Seasonal Affective Disorder winter type were included in the study (2007/2008). According to DSM-IV criteria only unipolar patients with a seasonal pattern were included. Identity of the patients was unknown to the technicians and investigators who isolated the RNA, processed it and further analyzed the data. The study was approved by the Medical Ethical Committee (MEC) of the University Medical Centre of Groningen (UMCG) and all patients gave written informed consent after full explanation of the study.

2.2. Power analysis gene expression and amendment approved by the MEC

We calculated that 36 responders to BLT would be necessary to meet the power criteria (power 90%; $\alpha = 0.05$; $D = 0.7$) (Cohen, 1969). To reduce the costs of the gene expression experiments we intended to pool equal amounts of RNA from 4 patients. This increases the effect size by a factor 2 and requires only 4 additional patients to meet the power criteria (Cohen, 1969). Because the acute response rate of BLT is approximately 80% (Gordijn et al., 2012; Meesters et al., 1995) it was considered necessary to include 50 patients at the start of the study.

After the winter season it became clear that we had not succeeded in including the required 50 patients, mainly because the major part of the regular patients did not consent with the study, possibly out of discomfort for the genetic part of the study. When we discussed this with the MEC, they allowed us to process the data of a smaller group of patients, without pooling the samples, and to present the results as a pilot study. Important arguments were our hesitation to introduce an additional variable by extending the study with another year and the considerable reduction of (experimental) noise by using the metagene approach.

2.3. Inclusion and exclusion criteria

Patients aged between 18 and 65 years suffering from winter depression (DSM-IV-TR, unipolar depressive disorder with seasonal pattern, winter type) and a score > 18 on the questions of the SIGH-SAD scale on two subsequent occasions were included in the study, while patients suffering from other Axis-I disorders (DSM-IV-TR) or with an actual suicide risk were excluded. Patients undergoing other forms of therapy or suffering from somatic diseases that might deteriorate by BLT (Meesters and Letsch, 1998) were also excluded.

Patients were not exposed to increased amounts of light and underwent no other forms of therapy in addition to BLT in the present study.

2.4. Bright light therapy (BLT)

Patients with winter depression were exposed to 45 min of bright light (full spectrum without UV with an intensity of 10,000 lx) in the morning for 5 successive days. The bright light apparatus was from SunBox, type Sun Square. Distance from the eyes was approximately 25 cm. BLT is the standard treatment at the winter depression outpatient clinic of the UMCG. Adverse effects are generally mild (Levitt et al., 1993; Labbate et al.,1994; Kogan and Guilford, 1998; Meesters and Van den Hoofdakker, 1998a,b).

2.5. Measures

M.I.N.I. Mini International Neuropsychiatric Interview, DSM-IV (Lecrubier et al., 1998) Dutch version 5.0.0.
This semi-structured and standardized interview is used to diagnose depression according to DSM-IV criteria.

SIGH-SAD Structured Interview Guide for the Hamilton Depression Rating Scale, 24 items version (Williams et al., 1994).
The SIGH-SAD measures severity of winter depression and is the main parameter of effect size in this study. Seventeen questions measure symptom severity of depression (Hamilton Depression Rating Scale) while the remaining questions assess typical symptoms of winter depression such as increased need for sleep and food.

2.6. Collection of blood

Blood was collected in Paxgene® tubes on three occasions at the same time of day (9.00 AM) in winter prior to and following BLT and in the subsequent summer, and stored at −20 °C.

2.7. Isolation of RNA

RNA was isolated at the Laboratory Medicine of the UMCG using the PAXgene™ Blood RNA Kit (Ref. 762174). The amount of RNA was measured using the Nanodrop method (NanoDrop ND 1000, Isogen, De Meern, the Netherlands). RNA was stored at −80 °C until shipment to Service XS (Leiden, the Netherlands).

2.8. Gene expression analysis

Quality of the RNA was evaluated at Service XS (Leiden, the Netherlands) using the Agilent Bioanalyzer (lab on chip). All samples passed the quality control test.

The Illumina® TotalPrep™ RNA amplification kit (Ambion, art. No. AM-IL1791) was used to synthesize biotine labeled cRNA. Concentration of the labeled cRNA was measured using the NanoDrop ND-1000 spectrophotometer. The amount of biotinylated cRNA that was hybridized onto the Illumina® HumanHT-12 v3 Expression BeadChip was 750 ng. It is important to note that RNA samples were not pooled in this pilot study as requested by the MEC (see Section 2.3). Illumina's GenomeStudio Software v1 with the default settings advised by Illumina was used for Gene Expression analysis. Quality control data were within specifications, except for one probe displaying too low average signal intensity. The raw optical data were sent to the University Centre for Psychiatry in Groningen for further analysis.